REMARKS

Claims 1-35 and 46-65 are pending in the application. Claims 31-34 are withdrawn from examination as directed to a non-elected invention. Claims 13-15, 17, 22-30, and 60-63 are withdrawn from examination as directed to non-elected species. Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are presented for examination on the merits to the extent that they read on the elected species, designated as human/human chimeric RSV with a G heterologous gene or gene segment. By this submission, claim 35 has been amended for clarity in accordance with the Office's suggestions. Also by this submission, the specification has been amended to expand the priority claim in the application to embrace earlier parental filings. All of the amendments presented herein are fully supported by the disclosure and no new matter has been added to the application.

Drawings

Applicants note the Draftsperson's objection to Figure 26. Submitted herewith is a substitute page for Figure 26, which provides the figure in a revised orientation to comply with the Draftsperson's objections. Entry of the figure is respectfully requested.

Claim Objections

Claim 35 is objected to under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. In accordance with the Office's suggestions, Applicants have amended the subject claim for clarity to place the claim in proper dependent form. In particular, amended claim 35 is now drawn to the chimeric respiratory syncytial virus of claim 1 "which is a complete virus". As is clearly denoted in the specification and original claims, the "respiratory syncytial virus" of claim 1 is directed to an isolated infectious viral particle which comprises at a minimum the N, P, L and polymerase elongation factor proteins. As such, this basic virus particle is viable and infectious without the inclusion of non-essential components of a "complete" RSV. In contrast, as is also disclosed in the specification, it is within the scope of the invention to provide recombinant RSV that comprise essentially complete viruses, i.e., with all essential viral components and further including non-essential components as found in a complete, e.g., wild-type, RSV. Clearly representative of these teachings, the specification teaches that a number of non-essential genes, for example the SH, NS1 and NS2 genes, "can be ablated or

otherwise modified in a chimeric RSV to yield desired effects on virulence, pathogenesis, immunogenicity, and other phenotypic characters. For example, ablation by deletion of a non-essential gene such as SH results in enhanced viral growth in culture." (page 47, lines 29-35).

In view of the foregoing clarifying amendment and comments, the objection to claim 35 is believed to be obviated.

Patentability Under 35 U.S.C. § 112, Second Paragraph

Claims 5, 7, and 8-10 stand rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. Specifically, the Office states that claims 5, 7, and 8 recite a chimeric RSV "with a heterologous gene encoding a G glycoprotein or immunogenic epitope thereof." The Office contends that the disclosure "fails to teach what is encompassed within the metes and bounds of an immunogenic epitope of RSV G protein", and that on this basis the metes and bounds of the claimed invention cannot be determined. Applicants respectfully traverse.

The claims at issue (see, e.g., claim 5) are directed to chimeric RSV comprising in relevant part "a partial or complete RSV genome or antigenome of one human RSV strain or subgroup virus combined with a heterologous gene or gene segment of a different human RSV strain or subgroup virus to form a chimeric RSV genome or antigenome" . . . "wherein the heterologous gene or gene segment encodes a RSV F, G or SH glycoprotein or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof." Applicants' disclosure clearly conveys the metes and bounds of this alternative subject matter to the skilled artisan.

The Office recognizes that Applicants' disclosure clearly conveys the metes and bounds of claimed subject relating to substitution of an entire, heterologous glycoprotein (exemplified by the representative species under examination comprising the G glycoprotein). Further, the Office recognizes that the disclosure adequately conveys substitutable heterologous glycoprotein domains (e.g., a cytoplasmic domain, transmembrane domain, or ectodomain) within a background comprising a partial glycoprotein of a different human RSV subgroup or strain to form a chimeric glycoprotein. The only objection therefore is directed to the language "immunogenic epitope", and it is respectfully submitted that this term also is widely recognized and understood in the art, whereby Applicants have also conveyed possession of this aspect of the invention to the skilled artisan.

Applicants' disclosure pertaining to the incorporation of one or more heterologous gene segment(s) encoding one or more heterologous "immunogenic epitopes" (implicitly contained

in an "immunogenic domain" or "immunogenic region" of the G protein) is extensive, as provided in the specification, e.g., at p. 9, lines 11-35 (concluding with the statement that heterologous "immunogenic proteins, domains and epitopes are particularly useful within chimeric RSV because they can generate novel immune responses in an immunized host"); at p. 19, lines 18-28 ("chimeric RSV of the invention can individually elicit a monospecific immune response or a polyspecific immune response"); at p. 30, lines 28-38 ("the recipient genome or antigenome acts as a vector to import and express heterologous genes or gene segments to yield chimeric RSV that exhibit novel structural and/or phenotypic characters); at p. 31, lines 15-27 ("An entire G or F gene, or a gene segment encoding a particular immunogenic region thereof, from one RSV strain is incorporated into a chimeric RSV genome or antigenome cDNA by replacement of a corresponding region in a recipient clone of a different RSV strain or subgroup, or by adding one or more copies of the gene, such that several antigenic forms are represented"); at p. 32, lines 12-22 ("a variety of gene segments provide useful donor polynucleotides for inclusion within a chimeric genome or antigenome to express chimeric RSV having novel and useful properties. Thus, heterologous gene segments may beneficially encode a cytoplasmic tail, transmembrane domain or ectodomain, an epitopic site or region, a binding site or region, an active site or region containing an active site, etc., of a selected protein from one RSV"); at p. 33, lines 11-19 ("counterpart gene segments may encode a common structural domain of a protein, such as a cytoplasmic domain, transmembrane domain, ectodomain, binding site or region, epitopic site or region etc. Typically, they will share a common biological function as well. For example, protein domains encoded by counterpart gene segments may provide a common membrane spanning function, a specific binding activity, an immunological recognition site, etc.").

The meaning of the term "heterologous gene segment encoding a heterologous immunogenic epitope" is thus clearly conveyed to the skilled artisan. No lack of clarity is imposed by use of the art recognized term "immunogenic epitope", which ordinarily is understood to represent a minimal structural unit within a protein, or within a known antigenic domain or region of a protein. Identification of immunogenic epitopes was also widely understood and practiced, for example by various known methods of "epitope mapping" using e.g., monoclonal antibodies and/or truncated or mutant peptides or proteins to pinpoint immunogenic epitopes within proteins.

The artisan's wide use and understanding of the term "immunogenic epitope" was well established at the time of the present invention, particularly in relation to the G protein of RSV and other related viruses. For example, in one review entitled "Antigenic structure, evolution and

immunobiology of human respiratory syncytial virus attachment (G) protein", J. Gen. Virol. 78:2411-2418, 1997 (copy will be provided under separate cover), Melero and colleagues report as follows:

> A large number of murine monoclonal antibodies have been raised against the G glycoprotein of HRSV and they have been used to classify viral isolates into two antigenic groups, A and B (Anderson *et al.*, 1985 ; Mufson *et al.*, 1985 ; GarciaBarreno *et al.*, 1989). By testing the reactivity of monoclonal antibodies with a large panel of viral strains, three types of epitope have been identified in the G protein: (i) *conserved* epitopes that are present in all the HRSV isolates, (ii) *group specific* epitopes shared by all viruses of the same antigenic group and (iii) *strain-specific* or *variable* epitopes that are present in certain isolates of the same antigenic group (Martinez et al., I997).

This passage makes it clear that the term "immunogenic epitope" as applied to the G protein of RSV was widely used and specifically understood by the skilled artisan at the time of Applicants' invention. Moreover, as discussed in further detail below, extensive epitope mapping of the G protein was widely undertaken and yielded detailed information concerning a wide array of specific epitopes, including such detail as assigning the evolutionary status of these specific epitopes among the groups characterized by Melero et al. as *conserved*, *group specific*, *strain-specific* or *variable* epitopes. Based on this and other evidence presented below, Applicants respectfully submit that the rejection of claims 5, 7, and 8-10 under 35 U.S.C. 112, second paragraph, for alleged indefiniteness has been overcome.

Patentability Under 35 U.S.C. § 112, First Paragraph

Claims 5, 7, and 8-10 stand rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. The Office recognizes that the specification is "enabling for chimeric RSV with a heterologous gene encoding a G glycoprotein, cytoplasmic domain, transmembrane domain, or ectodomain." However, it is asserted that the specification "does not reasonably provide enablement for chimeric RSV with a heterologous gene encoding an immunogenic epitope of a G glycoprotein." Applicants respectfully traverse this ground of rejection and submit that the disclosure, viewed from the perspective of the skilled artisan apprised of knowledge widely known in the art, fully enables the subject matter of the claims presented for review.

Specific grounds for the Office's rejection under this section of the Patent Act are stated in reference to the "nature of the invention." The sole evidentiary reference in this context is a

conclusory statement that the specification allegedly "fails to teach immunogenic epitopes of the G glycoprotein." In rebuttal, Applicants respectfully submit that the foregoing discussion clearly establishes that their specification teaches these antigenic structural features in sufficient detail to convey their possession to the skilled artisan.

With regard to the identification of specific immunogenic epitopes commensurate with the scope of the claims, this is clearly enabled by the broad disclosure of the specification and the many references incorporated therein that detail mapping of the RSV genome and protein structure-function analyses. Specific references describing RSV glycoprotein structure-function, and construction of chimeric viruses "to carry antigenic determinants between viral strains" are provided, e.g., at page 2, lines 22-30; and page 7, lines 2-29. The nature and extent of enabling disclosure in this context is further evinced by the myriad publications on these subjects prior to Applicants' filing date that comprise the "state of the art" and reflect the level of "predictability in the art"—which are two key components of enablement review to which the Office refers in support of the rejection.

In relation to these review criteria, the Office characterizes the "*state of the prior art and the predictability or lack thereof in the art*" with a conclusory statement, as follows:

> The art teaches that the complete G glycoprotein is immunogenic, but does not teach immunogenic epitopes thereof (see for example, Oien et al., Vaccine 1993, 11(10) p1040-8, especially the abstract).

In fact, the art pertaining to the invention at the time of Applicants' filing date was replete with published structure-function analyses of RSV glycoproteins, particularly with references describing epitope mapping and phylogentic comparison of immunogenic regions and epitopes for the RSV G glycoprotein. In evaluating these publications, which are summarized in detail below, the Office is urged to consider that, to the extent the teachings of these references establish information that is "widely known in the art", they need not be incorporated in Applicants disclosure, and are preferably omitted therefrom. This long standing legal rule was originally stated in the case of Webster Loom Co. v. Higgins et al., 105 U.S. 580, 586; 26 L.Ed. 1177, ____ (1881), as follows:

> That which is common and well known is as if it were written out in the patent and delineated in the drawings.

See also, In re Johnson, 127 USPQ 216, 218 (CCPA 1960).

In the instant case, numerous publications relating to epitope mapping for RSV glycoproteins established, at the time of the invention, that the RSV G protein possessed unique

structural and functional properties that made this protein amenable to such modifications as, natural mutations, deletions, truncations, and other manipulations--without losing function as an immunogen, and/or without disrupting infectivity and viability of the modified or mutated protein or (biologically-derived) virus. It should be noted in this context that persons of ordinary skill in the art at the time this claimed invention was made did not have the benefit Applicants' disclosure of methods to recover RSV from cDNA as presented in the issued parent disclosure (U.S. Patent No. 6,264,957, issued July 24, 2001) to which the instant application, as amended herein, claims priority. Thus, while these studies show the amenability of the RSV G protein to major structural modifications commensurate with those contemplated herein, chimeric viruses with recombinant modifications, as presently claimed, were not attainable.

The initial study pointing to a unique structure of the RSV G protein was the first sequence publication for this protein, which referred to G as an "unusual type of viral membrane protein" (Wertz et al., Proc. Nat. Acad. Sci. USA 82:4075-4079, 1985 (copy will be provided under separate cover). In particular, the G protein was shown to have an unusual structure, composed mainly of linear epitopes, in contrast to a highly folded structures in which the majority of epitopes are "conformational" (i.e., they comprise residues that are not all contiguous in the linear amino acid sequence but are brought into proximity by the folded structure) epitopes. This uniquely flexible architecture is reflected in additional studies, described below, where peptide fragments of G are shown to be highly immunogenic.

The "linear" nature of the RSV G protein was first suggested by its unusual amino acid structure, similar to that of mucins which are long, linear proteins (Wertz et al., ibid, Johnson et al, Proc. Nat. Acad. Sci. USA 84:5625-5629, 1987 (copy will be provided under separate cover). One important functional correlate of this unique structure is that G-specific antibodies remain highly reactive against the protein, even when it is denatured, truncated, conjugated, or otherwise significantly modified or mutated from its native sequence (see below).

The linear structure of the RSV G protein (ascribed to most of the G protein's immunogenic ectodomain) means that many of its epitopes can be represented by short linear peptide fragments. In addition, the protein itself is amenable to engineering in the manner contemplated within the present disclosure, since it lacks a complex folding requirement that render other glycoproteins more sensitive to amino acid substitutions.

With respect to the identification of specific epitopes of the RSV G protein for use within the claimed, chimeric RSV, these had been mapped extensively by the time of the

invention. One important series of studies involved the direct identification of epitopes by studying the antigenicity , immunogenicity and protective efficacy of synthetic peptides representing segments of the G protein. For example, Norrby et al. (Proc. Nat. Acad. Sci. USA 84:6572-6576, 1987 (copy will be provided under separate cover) performed a comprehensive study in which overlapping peptides spanning the complete extracellular domain of G were analyzed for epitopes. This report identified a number of specific sites that reacted with murine monoclonal antibodies as well as human convalescent sera. A subsequent study by the same group provided evidence of residues 174-188 as comprising an immunodominant epitope (Akerlind-Stopner, J. Virol. 64:5143-5148, 1990 (copy will be provided under separate cover). Another group of investigators showed that a different peptide contained an epitope within residues 174-187 that induced protective immunity against RSV infection in mice (Trudel et al., Virology 185:749-757, 1991 (copy will be provided under separate cover). Yet another group of researchers identified a third major epitope within amino acids 187-200 of the RSV G protein (Garcia-Barreno et al., J. Gen. Virol. 73:2625-2630, 1993 (copy will be provided under separate cover).

Additional experiments mapped epitopes by sequencing virus variants selected for their resistance to monoclonal antibodies directed against the G protein. This approach has the advantage of identifying epitopes in the context of a complete protein expressed in a viable, infectious virus. These studies also identified a major, broadly cross-reacting antigenic site in the middle of the G protein molecule corresponding to the 187-200 epitope identified above (Garcia-Barreno et al., EMBO J. 9:4181-4187, 1990 (copy will be provided under separate cover). A second study of additional G anitibody-resistant RSV mutants provided independent evidence that residues in the middle of the molecule, spanning residues 187-200 and including positions to either side, constituted major, broadly cross-reacting epitopes (Rueda et al., Virology 198:653-662, 1994 (copy will be provided under separate cover). Yet another study mapped an additional epitope to the last 11-42 amino acids of the G glycoprotein (Rueda et al., J. Virol. 65:3374-3378, 1991 (copy will be provided under separate cover).

In summary, these studies provided direct evidence of a number of major antigenic epitopes in the RSV G protein that were shown to be involved in inducing protective immunity. Importantly, these studies also provided evidence that short segments of G can be highly efficient immunogens in the absence of major flanking portions of the protein.

Evidence that the G protein is amenable to chimeric engineering within the methods of the invention is also found in the very high degree of amino acid sequence diversity among different RSV strains and subgroups (Johnson et al, ibid). The patterns of evolutionary nucleotide changes found among different RSV strains and subgroups show little evidence of structure-function constraints leading to canonized amino acid sequence elements (Johnson et al, J. Gen. Virol. 70:1539-1547, 1989; Sullender et al., J. Virol. 65:5425-5434, 1991 (copies will be provided under separate cover). These features complement the unique extended, linear structure of the G protein as structural aspects that render render the G protein uniquely amenable to modification within the methods of the invention.

Even more powerful evidence of G protein structural flexibility within the methods of the invention (particularly for swapping immunogenic domains and epitopes between different subgroups or strains) comes from the above-mentioned studies of monoclonal antibody-resistant mutants. These studies involving truncations or frame shifts showed that deletions and/or substitutions ranging in size up to 46% of the entire G protein ectodomain can be accommodated without loss of viral infectivity (Garcia-Barreno et al., EMBO J. 9:4181-4187, 1990; Rueda et al, Virology 198:653-662, 1994; Rueda et al, J. Virol. 65:3374-3378, 1991 (copies will be provided under separate cover). In other studies, truncation mutants of the 298-amino acid G protein were made in which the N-terminal 71, 180 or 230 amino acids were fused to a malarial epitope, demonstrating that even drastically-truncated versions of G in combination with heterologous epitopes could be expressed and later shown to be transported to the cell surface (Viijaya et al, Mol. Cell. Biol. 8:1709-1714, 1988 (copy will be provided under separate cover). Yet another study demonstrated the construction of functional chimeras between the RSV G protein and the unrelated parainfluenza virus type 3 HN protein (Collins, J. Virol. 64:4007-4012, 1990 (copy will be provided under separate cover). Finally, in an even more closely related study to the present invention, Sullender et al. showed that different, epitope-containing fragments of the RSV G protein could be readily swapped into a corresponding G protein in a different RSV subgroup to yield novel immunogenic, chimeric G proteins (Virology 209:70-79, 1995 (copy will be provided under separate cover). In relevant passages Sullender et al. teach that:

> The three regions exchanged in the modified cDNAs are shown. The three regions were designated A or B to indicate whether they were derived from the A or B group prototype G cDNAs. Region 1

(designated Al or B1, G protein amino acids 1 to 173) included the cytoplasmic tail, transmembrane domain, the first variable region in the ectodomain, and part of the central conserved region; region 2 (designated A2 or 132, amino acids 174 to 214 in the group A protein and 174 to 215 in the group B protein) included the remainder of the central conserved region; and region 3 (designated A3 or 63, amino acids 215 to 298 in the group A protein and amino acids 216 to 292 in the group B protein) included the second variable region in the ectodomain. The chimeric proteins resulting from the cDNA exchanges were designated A1A2B3, B1 B2A3, A1 B2B3, and B1A2A3. The truncated proteins were designated A1A2, 131132, A1, and 131 (Fig. 1 B). (at page 74, right column),

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In order to assess the capacity of the chimeric and truncated proteins to undergo protein folding and transport to the cell surface, expression of the proteins was assessed by cell surface immunofluorescence (Fig. 4). The prototype group A and group B, the four chimeric (Fig. 4A), and the four truncated proteins (Fig. 4B) were detected on the surface of transfected cells by immunofluorescence.

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The chimeric and truncated G proteins were tested for reactivity with MAbs in order to define the regions of the G protein which were required for the maintenance of reactivity with these antibodies. The MAbs were tested against the expressed proteins by immunofluorescence on acetone-fixed cells (results in Table 1). All of the group-cross-reactive MAbs reacted with the prototype G proteins and, with the exception of one MAb (130-5f), with all of the chimeric proteins. The truncated proteins A1A2 and 131 B2 also reacted with all of the cross-reactive MAbs except for MAb 130-5f, which did not react with the 1311132 protein. The truncated proteins A1 and B1 reacted with the group-cross-reactive MAbs 131-2g and 021 /1 G but not with the other group-cross-reactive MAbs.

The group A-specific MAbs reacted with proteins which contained regions A2 or A3 (Table 1). Some MAbs reacted with proteins B1Z2A3, A1A2B3, or A1A2, indicating a dependence on the A2 region. Others reacted with B1A1A3 or B1B2A3, indicating a dependence on the presence of the A3 region.

Further addressing the Office's stated grounds of rejection, the only publication cited by the Office pertaining to Applicants methods for constructing G protein chimeric viruses,

Oien et al, Vaccine 11:1040-1048, 1993, is respectfully submitted to be inapposite to the issue of enablement in the present application. In particular, this reference addresses "a chimeric glycoprotein FG_B" which is composed of the F glycoprotein from RSV subgroup A fused with a truncated G glycoprotein from RSV subgroup B. This model for protein engineering is clearly not comparable to the presently claimed subject matter. In particular, the engineered protein of Oien et al. is not a chimeric G glycoprotein composed of one or more heterologous epitopes from a G glycoprotein of a different RSV subgroup or strain. On the contrary, it is a fusion of an entirely distinct protein F from one RSV subgroup with a truncated G glycoprotein from a different RSV subgroup.

In summary, Applicants' diclosure, combined with the teachings represented in the foregoing publications and other "widely known" information available at the time of Applicants' disclosure, point to a high level of skill, predictability and guidance in the art pertaining to G protein epitope mapping, structure-function analysis and chimeric protein engineering. The foregoing examples identify specific epitopes and demonstrate detailed strategies by which linear domains containing one or more epitopes or protein domains can be substituted, modified or deleted within the methods of the invention. The examples also demonstrate methods by which the antigenicity, immunogenicity and protective efficacy of the resulting molecule can be assayed to show the success of chimeric engineering methods within the invention.

Double Patenting

Claims 1-12, 16, 18-21, *35,* 46-59, and 64-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 96-103, 131, and 15 1-153 of of copending Application No. 09/444,067 and claims 20, 31, and 56 of copending Application No. 09/444,221. The Office contends that, although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to chimeric human/human respiratory syncytial viruses of different subgroups (A and B) having a heterologous G gene.

Applicants note that this is a provisional obviousness-type double patenting rejection, and respectfully defers addressing the merits of the rejection until conflicting claims in one of the subject cases are in fact been patented.

Patentability Under 35 U.S.C. §§ 102 and 103

Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are rejected under 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over Randolph et al. (EPA 0 567 100).

The Office characterizes the claimed invention as being drawn to an isolated infectious chimeric respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, a RNA polymerase elongation factor, and a partial or complete genome of one human RSV strain combined with a heterologous gene of a different RSV strain, wherein the heterologous gene is the G gene and wherein the chimeric RSV is further modified by one or more attenuating mutations adopted from different biologically derived mutant RSV strains or stabilized by multiple nucleotide changes in the codon specifying the mutation, formulated in a dose of 10^3 to 10^6 PFU of attenuated virus. The claimed invention is further characterized as being drawn to immunogenic compositions comprising the virus for administration to the upper respiratory tract by spray, droplet or aerosol and to isolated polynucleotides comprising a chimeric RSV genome or antigenome of one human RSV strain (subgroup A) combined with a heterologous gene of a different RSV strain (subgroup B), wherein the heterologous gene is the G gene.

The Office relies on Randolph et al. for teaching vaccine compositions "comprising mutant RSV of subgroups A and B and nucleic acid molecules encoding the mutant RSV." The Office further cites Randolph et al. for teaching that both RSV subgroups are important respiratory pathogens, whereby effective vaccine compositions should protect against both groups, and that the immunogenic polypeptides of RSV include the G polypeptide. Allegedly included in Randolph's teachings is intranasal administration of an aerosol containing 10^6 PFU "of the infectious RSV" for eliciting systemic immunity."

In further discussion, the Office specifically cites Randolph et al. for teaching "human chimeric RSV in which the nucleic acid regions encoding one or more polypeptides of one of the RSV types (A or B) is substituted into the genome of the heterologous type".

In addition, the Office states that Randolph teach "the RSV as further comprising the N protein, the P protein, the L protein, and regulatory sequences."

Finally, the Office cites Randolph et al. for teaching "the RSV as also comprising one or more attenuating mutations adapted from biologically derived (cold-adapted or temperature-

sensitive) strains", and for disclosing that "attenuated RSV with multiple genetic lesions are more stable and have a reduced probability of reverting to wild type."

In summarizing the grounds for rejection, the Office asserts that:

> The vaccines comprising chimeric viruses and the nucleic acids taught by Randolph anticipate the claimed invention, or in the alternative, one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made immunogenic compositions comprising infectious human chimeric subgroup A/subgroup B viruses with the heterologous G gene and further comprising one or more attenuating mutations derived from biologically derived mutant strains based on the teachings of Randolph. (underscores added).

Applicants respectfully traverse the foregoing grounds for rejection and submit that the subject matter of claims 1-12, 16, 18-21, 35, 46-59, and 64-65 is neither anticipated by, nor rendered obvious by, the teachings of Randolph et al., EPA 0 567 100.

Analysis of the Randolph et al. teachings in the present context first requires reference to the controlling legal standards for review. It is well established that, whenever the office relies upon a reference to support a rejection under 35 U.S.C. § 102, it bears the initial burden of demonstrating that the reference discloses all of the elements and limitations of the claimed invention.

> The factual determination of anticipation requires the disclosure in a single reference of every element of the claimed invention. . . .[I]t is incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference. Ex Parte Levy, 17 USPQ2d, 1461, 1462 (Bd.Pat.App.Int. 1990).

In addition, each allegedly anticipatory reference must fulfill all of the written description and enablement requirements of 35 U.S.C. § 112.

> The standard for anticipation by patenting is the same one of a full enabling disclosure that applies to printed publications, i.e., it must disclose the invention in such full, clear and exact terms as to enable any person skilled in the art to which the invention relates to practice it. Electronucleonics Laboratories, Inc. et al. v. Abbot Laboratories, 214 USPQ 139, 147 (N.D. Ill. 1981) (underscore added, citations omitted).

As further explained by the Federal Circuit in In re Donohue, 226 USPQ 619, 621 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. (emphasis supplied).

In the instant case, the Randolph et al. publication clearly does not provide an enabling disclosure of how to make and use recombinant RSV vaccines recovered from polynucleotide contstructs (e.g., cDNA). On the contrary, the primary teaching from Randolph et al. in this context is a broad statement in the publication that the biologically derived mutant RSV A and mutant RSV B described therein are useful:

> (1) as live virus vaccines, (2) as a source of genetic material to give, enhance, or stabilize an attenuated phenotype of any RSV strain, (3) as a source of immunogenic polypeptide, (4) as a source of genetic material for recombinant expression of immunogenic polypeptides by a live virus or bacterial vector (e.g., baculovirus, vaccinia virus, adenovirus, attenuated Salmonella, (5) as viral vectors for expression of immunogenic proteins from other viruses, e.g., RSV F and G proteins, influenza HA and NA proteins, parainfluenza HN and F proteins, and (6) as a source of reagents to detect antibody in immunological assays or nucleic acid in enzyme amplification assays (e.g., polymerase chain reaction (PCR)). (p. 4, lines 12-20).

The statements in this passage that the Office has interpreted to relate to Applicants recombinant, chimeric RSV recovered from cloned nucleotide sequences are entirely prophetic and non-enabling. Clearly, the disclosure of Randolph et al. provides no recombinant RSV recovery methods nor recombinant RSV vaccines. On the contrary, the teachings of the reference are directed to the recovery of biologically derived, "cold adapted mutant RSV, specifically, mutant RSV of subgroup A and B." The reference in no way teaches how to use such biologically derived mutant viruses as "a source of genetic material for recombinant expression of immunogenic polypeptides by a live virus or bacterial vector (e.g., baculovirus, vaccinia virus, adenovirus, attenuated Salmonella)." It is even more apparent that the reference provides no guidance as to how to employ these biologically derived viruses as "viral vectors for expression of immunogenic proteins from other viruses, e.g., RSV F and G proteins, influenza HA and NA proteins, parainfluenza HN and F proteins." In fact, such biological viruses themselves cannot be used as "vectors" in the manner proposed. This purpose can only be achieved through a method for recovering recombinant RSV from cloned polynucleotides, as provided by Applicants' disclosure.

The prophetic statements of Randolph et al. regarding "recombinant expression of

polypeptides" and "viral vectors" in no way constitute an enabling disclosure of Applicants methods and compositions. In addition, these teachings fail to provide adequate motivation and guidance to render Applicants recovery of chimeric human RSV vaccines obvious. Indeed, the first successful recovery of RSV from cDNA was not available until Applicants' disclosure of this breakthrough technology in their priority U.S. Provisional Application No. 60/007,083, filed September 27, 1995 (succeeded by U.S. Patent Application No. 08/720,132, filed September 27, 1996, which issued July 24, 2001 as U.S. Patent No. 6,264,957). Accordingly, it is respectfully requested that the Office withdraw the rejection of claims 1-12, 16, 18-21, 35, 46-59, and 64-65 under 102(b) as anticipated by, or in the alternative under 35 U.S.C. 103(a) as obvious over, Randolf et al. EPA 0 567 100.

Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Murphy et al. (Virus Research 32:13-36, 1994) in view of Collins et al. (Proc. Natl. Acad. Sci USA, 92:11563-11567, 1995 (of record). Murphy et al. is cited for teaching live attenuated RSV vaccines, as well as the existence of two antigenically divergent RSV subgroups for which an effective vaccine should protect against both subgroups. Additionally, Murphy et al. is cited for teaching that vaccinia-recombinant viruses expressing either the F or the G glycoprotein of RSV induces almost complete resistance to RSV challenge in mice, and induces neutralizing antibodies in monkeys.

In further explanation, the Office notes that Murphy et al. teach RSV vaccines comprising biologically-derived live attenuated host range, cold passaged, and temperature-sensitive mutants. The biologically-derived attenuated mutants induce an immunogenic response without causing disease. It is noted by the Office that Murphy et al. "do not teach combining the gene encoding the G glycoprotein from one RSV subgroup with a partial or complete genome of an RSV of the second subgroup and do not teach integrating the mutations from the biologically-derived attenuated strains into the chimeric genome."

These critical secondary teachings are allegedly provided by the Collins et al. reference. In particular, Collins is relied upon by the Office for the foundational teaching of how to produce and recover "infectious human RSV from cloned cDNA", and how "such an approach makes it possible to introduce defined changes into infectious RSV."

Without further addressing the stated grounds for rejection, it is noted that the rejection is clearly obviated by the amendment herein changing the priority claim of the application. The present application has now been related back through the entire foundational lineage of the issued '957 patent, as discussed above. The Collins et al. article, published in December, 1995, post-

dates the earliest application filing date (U.S. Provisional Application No. 60/007,083, filed September 27, 1995) in this lineage. On this basis, the Collins et al. article cannot serve as a prior art reference in relation to the present claims. To the extent that Collins et al. teaches aspects of the instant invention, those aspects are fully disclosed in the above-identified earlier-filed priority application. Notably, the critical aspects of the priority disclosure emphasized by the Office in this regard, i.e., the ability to make "infectious human RSV from cloned cDNA", and a teaching that "such an approach makes it possible to introduce defined changes into infectious RSV", underscore the above-noted deficiencies of the Randolph et al. reference in terms of satisfying the present claims.

For the foregoing reasons, withdrawal of the rejection of claims 1-12, 16, 18-21, 35, 46-59, and 64-65 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Murphy et al. (Virus Research 32:13-36, 1994) in view of Collins et al. (Proc. Natl. Acad. Sci USA, 92:11563-11567, 1995, is earnestly solicited.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Respectfully submitted,

Date: **September 17, 2001**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

At page 1, following the heading "Related Applications", please delete the paragraph at lines 7-13 and replace it with the following paragraph that provides an amended priority claim in the application.

--The present application claims the priority benefit of, and is a continuation-in-part of, U.S. Patent Application No. 08/892,403, filed July 15, 1997, which is entitled to priority from U.S. Provisional Application No. 60/047,634, filed May 23, 1997, U.S. Provisional Application No. 60/046,141, filed May 9, 1997, and U.S. Provisional Application No. 60/021,773, filed July 15, 1996, each of which is incorporated herein by reference. The present application also claims the priority benefit of U.S. Patent Application No. 09/847,173, filed May 01, 2001, which is a divisional application of U.S. Patent Application No. 08/720,132, filed September 27, 1996, issued on July 24, 2001 as U.S. Patent No. 6,264,957, which is entitled to priority from U.S. Provisional Application No. 60/007,083, filed September 27, 1995, each of which is incorporated herein by reference.—

At page 33, line 17, please replace "may providing" with --may provide--.

IN THE CLAIMS:

35. (Amended) The chimeric RSV of claim 1 which is a complete virus.